A NOVEL SYNTHESIS OF PYRIDAZINONES: PREPARATION OF 3-[1-ARYL-6(1H)-PYRIDAZINON-3-YL]-2(1H)-QUINOXALINONES[1]

El Sayed H. El Ashry,[2] Yeldez El Kilany, and Adel Amer[3]

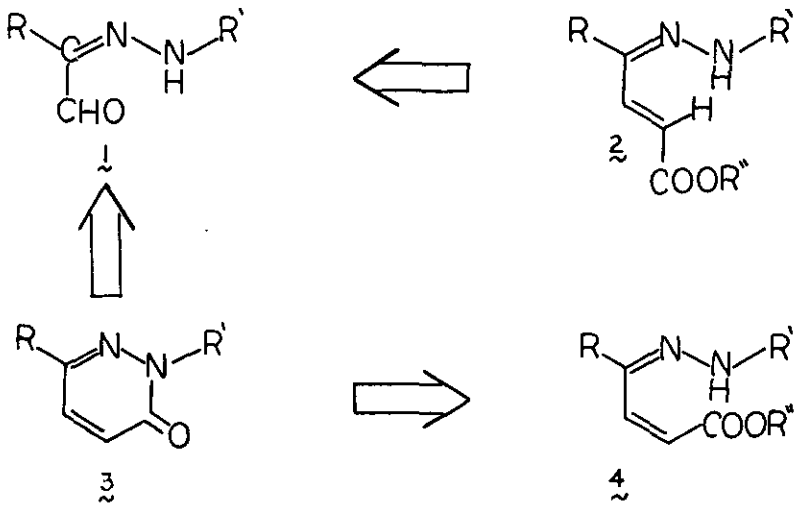
Department of Chemistry, Faculty of Science, Alexandria University, Alexandria, Egypt

Abstract — A novel approach for the synthesis of pyridazinones has been achieved by the reaction of α-formylhydrazones with carboethoxymethylidene triphenylphosphorane. The mode of the reaction was investigated and the structures were confirmed by both physical and chemical methods. Thus, 3-[1-aryl-6(1H)-pyridazinon-3-yl]-2(1H)-quinoxalinones (19) were prepared.

The pyridazinones are associated with analgetic, antihypertensive and antiinflammatory activities[4-10]. These biological properties as well as our interest in the synthesis of nitrogen heterocycles from carbohydrate precursors[11] draw our attention to find a new approach for the synthesis of pyridazinones.

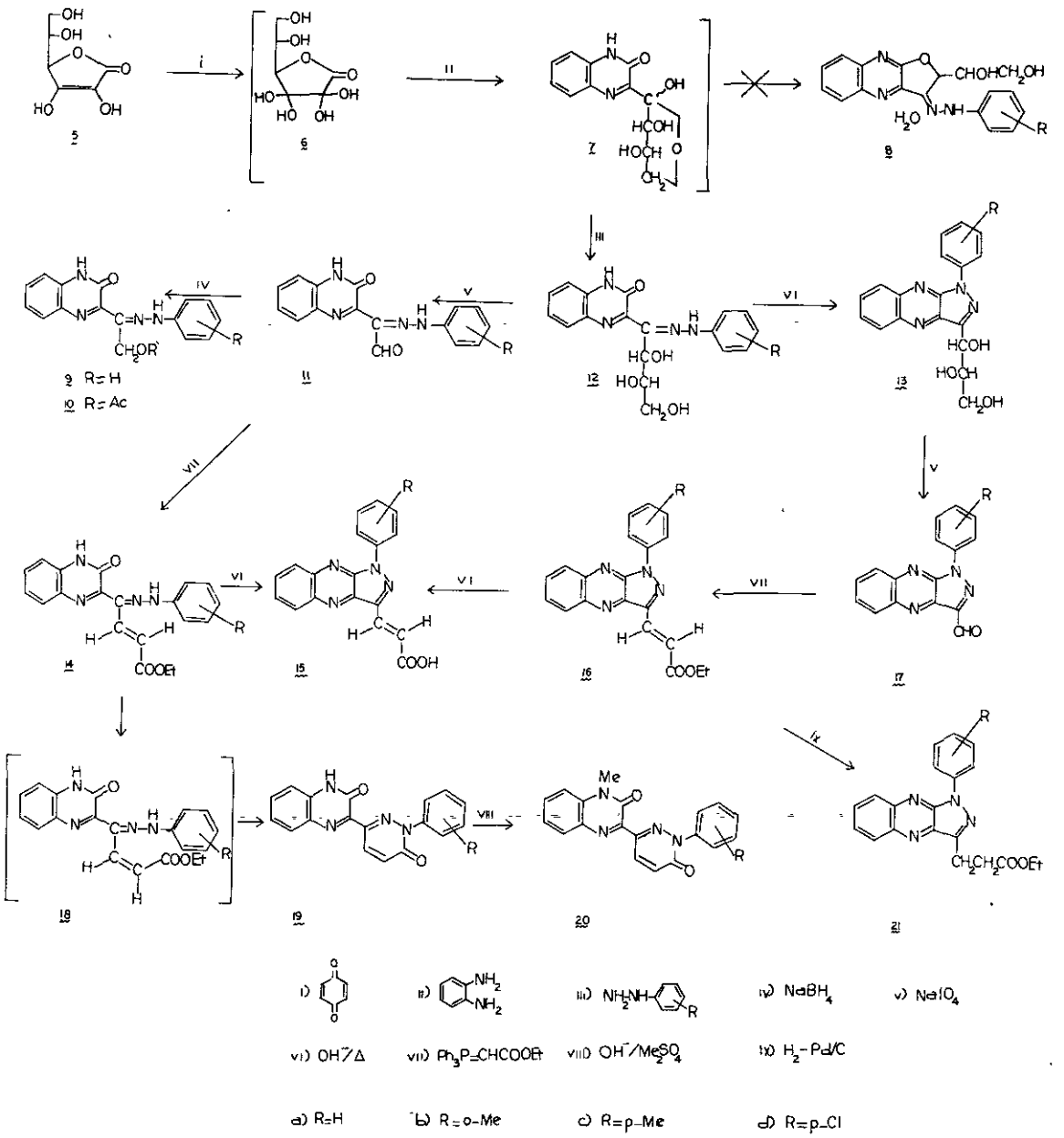
The structure of pyridazinone (3) indicates that it may possess a hidden α-formylhydrazone and an α,β-unsaturated carbonyl moieties. An approach to the elaboration of its carbon framework can be considered via the generation of the $=\overset{1}{C}-C=O$ moiety by reaction of the formyl group of an α-formylhydrazone (1) with carboethoxymethylidene triphenylphosphorane, the Wittig reaction, followed by cyclization. Bearing in mind that the stereochemical outcome of olefins prepared with the Wittig reagents should be anticipated to give in most cases the E-isomer, and by inspecting the model for the possibility of cyclization of the E- and Z-isomers

Scheme I

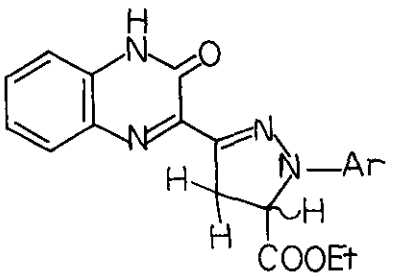


indicated that there was a possibility for the cyclization of the Z-isomer (4), but not the E-isomer (2) (Scheme I). Consequently, it is interesting to report on this phenomenon and on novel synthesis of the pyridazinone ring. When 3-(1-phenylhydrazonoglyoxal-1-yl)-2(1H)-quinoxalinone (11a) was allowed to react with carboethyoxymethylidene triphenylphosphorane in N,N-dimethylformamide (DMF), the product was found to be dependent on the reaction temperature, whereby two products could be obtained selectively. Namely, a red product (14a) was

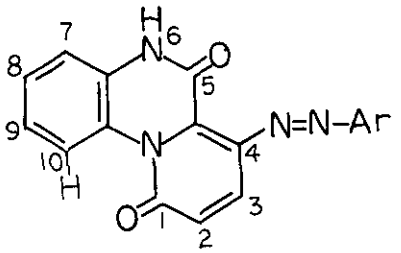
Scheme II



isolated in 73% yield upon carrying the reaction at 100°C, whereas a yellow product (19a) was isolated in 68% yield under reflux. On the other hand, compound (14a) could be transformed in 90% yield into the yellow compound (19a) under reflux in DMF (Scheme II). The structural assignments of the above two compounds (14a, 19a) were based on the elemental analyses and spectral data. ^{1}H-NMR spectral data showed the trans olefinic proton signals as the two doublets at δ 5.74 and 7.63 ppm with J=16 Hz for (14a) and the cis olefinic proton signals as the two doublets at δ 7.13 and 8.08 ppm with J=10 Hz for (19a). These data excluded the structures (22) and (23) for the above products (14a) and (19a), respectively. That is, compound (22) possesses the methylene and methine protons, while the C_{10}-H proton signal of (23) is expected to appear in a much lower magnetic field than the other aromatic protons, which is due to the anisotropy by the adjacent 1-carbonyl group[12,13]. Moreover, compound (19a) showed peaks at m/z 171 and 145 due to the ions resulting from the C-C bond fission between the two heterocyclic rings.



22



23

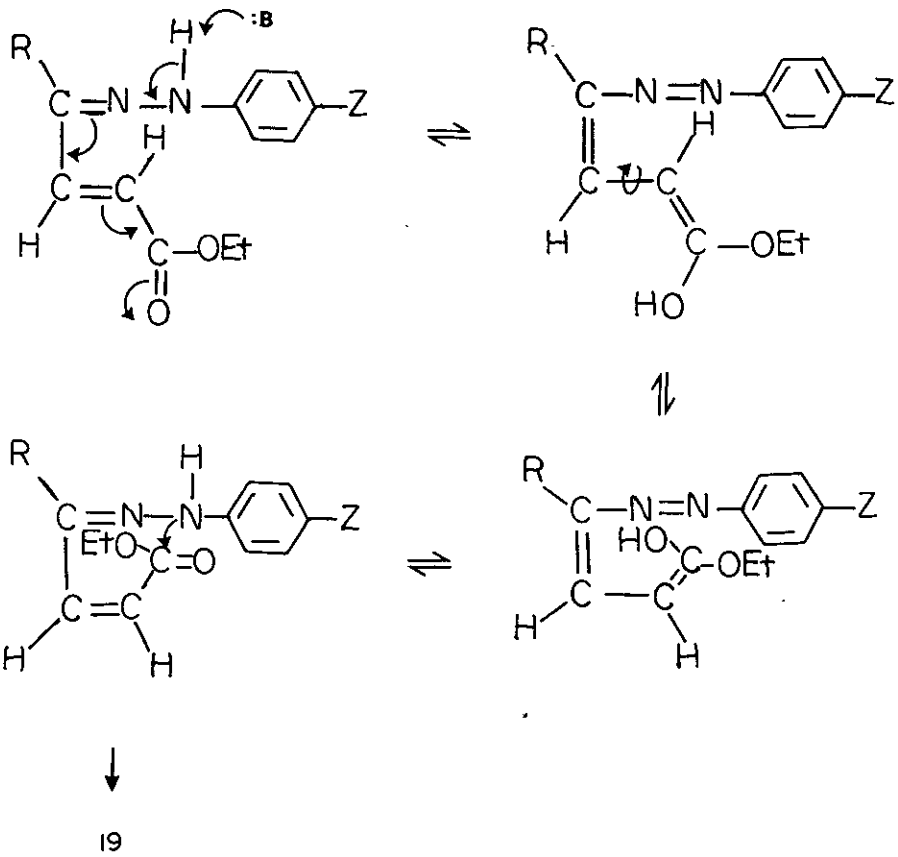
Treatment of (14a) with sodium hydroxide gave a mixture of two products which were identified as the pyridazinone (19a) and the flavazole (15a) in 1:3 ratio. This could be explained as two competing reactions occurring under the action of hot alkali; isomerization followed by cyclization gave (19a), and dehydrative cyclization accompanied with hydrolysis of the ester group afforded the acid (15a). The acid (15a) was alternately synthesized from the aldehyde (17a). The reaction of (17a) with carboethoxymethylidene triphenylphosphorane provided (16a), whose hydrolysis furnished (15a). Catalytic hydrogenation of the flavazole (16a) afforded the saturated derivative (21).

Methylation of (19a) with dimethyl sulfate in the presence of sodium hydroxide gave the corresponding N-methyl[11,14] derivative (20). Its mass spectrum showed the molecular ion peak at m/z 330 as the base peak. Prominent peaks [m/z 315 (RI = 3.6%); 302 (5.3); 301 (1.7); 274 (3.1) and 273 (4.8)] corresponding to ($M^{+\cdot}$ - Me), ($M^{+\cdot}$ - CO), ($M^{+\cdot}$ - NMe), ($M^{+\cdot}$ - 2CO), and ($M^{+\cdot}$ - CO - NMe) respectively were observed and strongly supported the N-methyl structure (20).

In order to study the scope of the reaction, the heterocyclization of the α-formylhydrazones (11) with

carboethoxymethylidene triphenylphosphorane was tried, whereby the pyridazinones (19) were successfully obtained. When the hydrazone residue has an electron withdrawing group such as the p-chlorophenyl, the cyclization to (19) was much more facile than the corresponding phenyl analog, possibly due to an increased rate of isomerization to the cis-ester, as shown in Scheme III. This results in a difficulty in isolating the corresponding olefin (14), whereas with electron donating groups the olefins could be easily isolated.

Scheme III



The starting α-formylhydrazones (11) required for the above study were prepared by a sequence of reactions. Oxidation of L-ascorbic acid with p-benzoquinone afforded dehydro-L-ascorbic acid (6). Treatment of compound (6) with o-phenylenediamine followed by the reaction with arylhydrazines provided the hydrazones (12), but not the dehydrated compound (8), as reported earlier[15-17]. Periodate oxidation of (12) gave the aldehydes (11) whose infrared spectrum showed the formyl and amide absorption bands at 1690 and 1660 cm^{-1}, respectively. The presence of the formyl function of (11) was further confirmed by reduction with sodium borohydride followed by acetylation to give the mono-acetyl derivative (10).

EXPERIMENTAL

General Methods: Melting points were determined with a kofler-block apparatus and are uncorrected. IR spectra were recorded with a Unicam SP-200 spectrometer, and ^{1}H-NMR spectra (for solution in dimethyl sulfoxide-d_6) with a JEOL-100 spectrometer, with tetramethylsilane as an internal standard. Chemical shifts are given in the δ scale. Mass spectra were recorded with an A.E.I. MS-902 instrument. Microanalyses were performed in the Chemistry Department, Faculty of Science, Cairo University, Cairo, Egypt.

3-[1-(o-Tolylhydrazono-L-threo-2,3,4-trihydroxybutyl]-2(1H)-quinoxalinone (12b). It was prepared by the standard procedure[15] to give the red-orange needles (yield: 65%); mp 185-187°C. IR(Nujol) 1655 (OCN) cm^{-1}. Anal. Calcd. for $C_{19}H_{20}N_4O_4$: C, 61.94; H, 5.49; N, 15.21. Found: C, 62.20; H, 5.60; N, 15.00.

3-[1-(o-Tolylhydrazono)glyoxal-1-yl]-2(1H)-quinoxalinone (11b). Compound (12b) was subjected to the action of sodium periodate using the reported procedure[17]. The product was crystallized from ethanol (yield: 78%): mp 255°C. IR (Nujol) 1660 (OCN), 1690 (CHO) cm^{-1}. Anal. Calcd. for $C_{17}H_{14}N_4O_2$: C, 66.65; H, 4.61; N, 18.29. Found: C, 66.50; H, 4.30; N, 18.60.

3-[2-Hydroxy-1-(o-tolylhydrazono)ethyl]-2(1H)-quinoxalinone (9b). It was prepared from (11b) by reduction with sodium borohydride using the reported procedure [17] to give red-orange needles (yield: 89%); mp 248-250°C. IR (KBr) 1675 (OCN) cm^{-1}. Anal. Calcd. for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.00; H, 5.50; N, 17.90.

3-[2-Acetoxy-1-(o-tolylhydrazono)ethyl]-2(1H)-quinoxalinone (10b). It was prepared by the acetylation[17] of compound (9b) with acetic anhydride in pyridine to give orange needles (yield: 79%); mp 212-215°C. IR (KBr) 1660 (OCN), 1730 (OAc) cm^{-1}: ^{1}H-NMR (DMSO-d_6): δ 2.03 (s, 3H, OAc), 3.3 (s, 3H, CH_3), 5.37 (s, 2H, CH_2), 7.3 (m, 8H, ArH), 12.7 (bs, 1H, NH), 14.37 (s, 1H, NH). Anal. Calcd. for $C_{19}H_{18}N_4O_3$: C, 65.13; H, 5.18; N, 15.99. Found: C, 64.80; H, 5.40; N, 15.80.

3-[2-(E-Carboethoxymethylidene)-1-phenylhydrazonoglyoxal-1-yl]-2(1H)-quinoxalinone (14a). A mixture of compound (11a) (0.58 g, 2 mmol) and carboethoxymethylidene triphenylphosphorane (0.7 g, 2 mmol) in N,N-dimethylformamide (10 ml) was heated on a boiling water bath for 4 h. The mixture was poured onto crushed ice and the product which precipitated was filtered off and washed with ethanol and dried (yield: 76%). Recrystallization from ethanol provided red needles: mp 208-210°C. IR (Nujol) 1665 (OCN and C=C), 1705 (COO) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.22 (t, 3H, J=8, CH_3), 4.15 (q, 2H, J=8, CH_2), 5.74 (d, 1H, J=16, -CH=), 6.9, 7.6 (2m, 10H, ArH and NH), 7.63 (d, 1H, J=16, -CH=), 12.67 (bs, 1H, NH). Anal. Calcd. for $C_{20}H_{18}N_4O_3$: C, 66.28; H, 5.01; N, 15.46. Found: C, 66.20; H, 4.90; N, 15.50.

3-[2-(E-Carboethoxymethylidene)-1-(o-tolylhydrazono)-glyoxal-1-yl]-2(1H)-quinoxalinone (14b). Compound (11b) was treated in a similar manner to the above, and the product was recrystallized from ethanol to give red needles (yield: 70%); mp 245°C. IR (KBr) 1660 (OCN and C=C), 1705 (COO) cm^{-1}. Anal. Calcd. for $C_{21}H_{20}N_4O_3$: C, 67.01; H, 5.36; N, 14.89. Found: C, 67.20; H, 5.30; N, 15.20.

3-[2-(E-Carboethoxymethylidene)-1-(p-tolylhydrazono)-glyoxal-1-yl]-2(1H)-quinoxalinone (14c). Compound (11c) was treated in a similar manner to the above, and the product was recrystallized from ethanol to afford red needles (yield: 76%); mp 216°C. IR (Nujol) 1665 (OCN and C=C), 1695 (COO) cm^{-1}. Anal. Calcd. for $C_{21}H_{20}N_4O_3$: C, 67.01; H, 5.36; N, 14.89. Found: C, 66.70; H, 5.10; N, 14.80.

3-[1-Phenyl-6(1H)-pyridazinon-3-yl]-2(1H)-quinoxalinone (19a). (a) A solution of compound (11a) (0.57 g, 2 mmol) and carboethoxymethylidene triphenylphosphrane (0.7 g, 2 mmol) in N,N-dimethylformamide (10 ml) was refluxed for 4 h. The reaction mixture was poured onto crushed ice and the product which precipitated was filtered off, washed with ethanol and dried. The brown product was recrystallized from ethanol to give yellow needles (yield: 68%); mp > 300°C. IR (Nujol) 1660; 1680 (OCN) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 7.1 (d, 1H, J=10, CH=), 7.5 (m, 9H, ArH), 8.1 (d, 1H, J=10, -CH=), 12.73 (bs, 1H, NH). Anal. Calcd. for $C_{18}H_{12}N_4O_2$: C, 68.35; N, 3.82; N, 17.71. Found: C, 68.20; H, 4.00; N, 17.40.

(b) A solution of compound (14a) (0.2 g, 0.55 mmol) in N,N-dimethylformamide (5 ml) was refluxed for 4 h. The reaction mixture was worked up as described above, and crystallization from ethanol afforded yellow needles (yield: 90%).

3-[1-(p-Chlorophenyl)-6(1H)-pyridazinon-3-yl]-2(1H)-quinoxalinone (19d). Compound (11d) was treated as described above, and yellow needles were obtained (yield: 62%; method a); mp 320°C. IR (KBr) 1660 (OCN) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 7.2 (d, 1H, J=10, -CH=), 7.6 (m, 8H, ArH), 8.1 (d, 1H, J=10, -CH=), 12.66 (bs, 1H, NH). Anal. Calcd. for $C_{18}H_{11}ClN_4O_2$: C, 61.6; H, 3.2; N, 16.0. Found: C, 61.50; H, 3.40; N, 15.70.

1-Methyl-3-[1-phenyl-6(1H)-pyridazinon-3-yl]-2(1H)-quinoxalinone (20a). A suspension of compound (19a) (0.33 g, 1 mmol) and sodium hydroxide (0.4 g) in methanol (10 ml) and water (15 ml) was warmed till clear solution was obtained. The reaction mixture was treated with dimethylsulfate (0.8 ml) and then allowed to stand overnight at room temperature. The product that separated out was filtered off, washed with water and dried. It was recrystallized from ethanol to furnish (20a) as colorless needles (yield: 58%); mp 226°C. IR (KBr) 1640, 1665 (OCN) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 3.68 (s, 3H, N-CH_3), 7.16 (d, 1H, J=10.4, -CH=), 7.41-7.84 (m, 9H, ArH), 8.02 (d, 1H, J=10.4, -CH=). Anal. Calcd. for $C_{19}H_{14}N_4O_2$: C, 69.08; H, 4.27; N, 16.96. Found: C, 68.90; N, 4.40; N, 16.80.

Reaction of carboethoxymethylidene triphenylphosphorane with 3-formyl-1-phenyl-1H-pyrazolo[3,4-b]quinoxaline (17a). Carboethoxymethylidene triphenylphosphorane (0.35 g, 1 mmol) was added to a solution of (17a) (0.27 g, 1 mmol) in N,N-dimethylformamide (20 ml), and the solution was refluxed for 4 h. The reaction mixture was processed by a usual manner, and recrystallization from ethanol gave yellow neddles (yield: 83%); mp 150°C. IR (Nujol) 1640 (C=C), 1705 (COO) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.13 (t, 3H, J=5, CH_3), 4.13 (q, 2H, J=5 Hz, CH_2), 7.9 (m, 11 H, ArH and CH=CH). Anal. Calcd. for $C_{20}H_{16}N_4O_2$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.60; H, 4.50; N, 16.20.

1-Phenyl-1H-pyrazolo[3,4-b]quinoxaline-3-Z-propenoic acid (15a). A suspension of compound (16a) (0.2 g, 0.58

mmol) in 0.01 N sodium hydroxide (50 ml) was refluxed for 4 h. The reaction mixture was cooled and neutralized with acetic acid. The product was recrystallized from ethanol to afford yellow needles (yield: 87%); mp 302-305°C. IR (KBr) 1635 (C=C), 1695 (COO) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 7.7 (m, 11H, ArH and CH=CH), 12.67 (bs, 1H, COOH). Anal. Calcd. for $C_{18}H_{12}N_4O_2$: C, 68.35; H, 3.82; N, 17.71. Found: C, 68.30; H, 3.70; N, 18.10.

Hydrolysis of compound (14a). A suspension of compound (14a) (0.3 g, 0.83 mmol) in 0.01 N sodium hydroxide (50 ml) was refluxed for 4 h. The reaction mixture was cooled and neutralized with acetic acid. The product was fractionally crystallized from ethanol to give yellow needles; mp 302-305°C, which did not show a melting point depression when mixed with compound (15a). The other compound was obtained from the mother liquor after concentration and was found to be identical with compound (19a).

Ethyl 1-phenyl-1H-pyrazolo [3,4-b] quinoxaline-3-propanoate (21a). A solution of compound (16a) (0.2 g, 0.58 mmol) in ethanol (100 ml) was added 5% Pd/C (0.05 g). The mixture was hydrogenated under the atmospheric pressure till the absorption of hydrogen was stopped. The mixture was filtered and the ethanolic solution was concentrated. The product was recrystallized from ethanol to provide lemon-yellow crystals (yield: 95%); mp 140°C. IR (KBr) 1705 (COO) cm^{-1}. Anal. Calcd. for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.18. Found: C, 69.50; H, 5.10; N, 16.00.

REFERENCES

1. Heterocycles from Carbohydrate Precursors, Part 44. For Part 43, see E. S. El-Ashry, Y. El-Kilany and H. Abdel Hamid, Carbohydr. Res., submitted for publication; for preliminary results of the present work, see E.S.H. El Ashry, M. M. Abdel Rahman, Y. El Kilany and Adel Amer, Carbohydr. Res., 1981, 86, C-5.
2. To whom correspondence should be addressed.
3. Present address: Department of Chemistry, University of Cincinnati, Cincinnati, Ohio, USA.
4. M. Tisher and B. Stansvnik, Advan. Heterocycl. Chem., 1968, 9, 211.
5. F. W. Mason and D. L. Aldous in R. N. Castle (Ed.), Heterocyclic Compounds, Vol. 28, Interscience, New York, 1973, p. 23.
6. Mitsui Toatsu Chemicals, Inc. Jpn. Kokai Tokkyo Koho Jap. Pat. 59 53,482; Chem. Abstr., 1984, 101, 90955W.
7. S. P. Breukelman, G. Meakins and A. M. Roe, J. Chem. Soc. Perkin Trans. I, 1985, 1627.
8. I. Sircar, B. Duell, G. Robowski, J. A. Bristol and D. B. Evans, J. Med. Chem., 1985, 28, 1405.
9. M. Takaya, M. Sato, K. Terashima and H. Tanizawa, J. Med. Chem., 1979, 22, 53.
10. G. Y. Lesher, U.S. Pat. 4,305,943, Dec. 1981.
11. E.S.H. El Ashry, Advan. Chem. Series, Am. Chem. Soc., 1982, 200, 1979, and references therein.
12. N. Kawahara, T. Nakajima, T. Itoh and H. Ogura, Heterocycles, 20, 1721 (1983).

13. N. Kawahara, T. Nakajima, T. Itoh, H. Takayanagi and H. Ogura, Chem. Pharm. Bull., 32, 1163 (1984).

14. K. Makino, G. Sakata, K. Morimoto and Y. Ochiai, Heterocycles, 23, 2025 (1985).

15. E.S.H. El Ashry, I. El Kholy and Y. El Kilany, Carbohydr. Res., 1978, 64, 81.

16. E.S.H. El Ashry, M.M.A. Abdel Rahman, M.A.M. Nassr and Adel Amer, Carbohydr. Res., 1978, 67, 403.

17. E.S.H. El Ashry, I. El Kholy and Y. El Kilany, Carbohydr. Res., 1978, 67, 495.

Received, 19th March, 1986